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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MASAHIRO KAKEHI, YOSHIHIRO USUDA, YUKIKO TABIRA, and SHINICHI SUGIMOTO

Appeal 2008-5697[1]
Application 10/798,339
Technology Center 1600

Decided:[2] March 24, 2009

Before DEMETRA J. MILLS, LORA M. GREEN, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] Heard March 19, 2009.

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

STATEMENT OF CASE

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

The following claim is representative.

9. A method for producing nucleoside 5'-phosphate ester, comprising the steps of culturing a bacterium belonging to *Escherichia coli* having an ability to produce nucleoside 5'-phosphate ester, in which expression of *ushA* gene and *aphA* gene is decreased as compared to a wild type strain by mutating or disrupting the *ushA* gene and the a*phA* gene, in a medium to produce and accumulate nucleoside 5'-phosphate ester in a medium, and collecting the nucleoside 5'-phosphate ester from the medium, wherein the nucleoside 5'- phosphate ester is selected from the group consisting of inosine 5'-phosphate ester and guanosine 5'-phosphate ester, and wherein the 5'-nucleotidase activity in the periplasm is substantially eliminated.

Cited References

Matsui et al.	EP 1 004 663 A1	May 31, 2000

Thaller et al., *Identification of the gene (aphA) encoding the class B acid phosphatase/phosphotransferase of Escherichia coli MG1655 and characterization of its product,* 146 FEMS MICROBIOLOGY LETTERS 191-198 (1997).

A. Cowman and I.R. Beacham, *Molecular cloning of the gene (ush) from Escherichia coli specifying periplasmic UDP-sugar hydrolase (5'-nucleotidase),* 12 GENE 281-286 (1980).

Grounds of Rejection

1. Claims 9, 13, and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Thaller et al. alone or in view of Cowman et al.

2. Claims 9 and 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Thaller et al. alone or in view of Cowman et al. and further in view of Matsui et al.

ISSUE

The Examiner concludes that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce *E. coli* mutants having non-functional, for example, disrupted *ush*A gene and *aph*A gene. The motivation to produce such mutants is provided by Thaller et al. who teach 5'-nucleotide dephosphorylating activity of *ush*A gene and *aph*A gene. Mutants with disrupted *ush*A gene and *aph*A gene would have a higher yield of 5'-nucleotides.

(Ans. 4.)

Appellants contend that there is no teaching in Thaller or Cowman that "decreasing expression of the gene would lead to enhanced production of nucleoside 5'-phosphate esters." (App. Br. 3.) Appellants further argue that neither Thaller nor Cowman, either alone or in combination, "suggest that decreasing expression of *ushA* gene and *aphA* gene or disrupting those genes would substantially eliminate the 5'-nucleotidase activity in the periplasm, as claimed." (*Id.* at 4.)

The issue is: Does the combination of Thaller with Cowman disclose or suggest a method that results in a decrease in *ushA* gene and *aphA* gene as compared to a wild type and wherein the 5'-nucleotidase activity in the periplasm is substantially eliminated?

FINDINGS OF FACT

1. Claims 9, 13, and 14 are rejected under 35 U.S.C. §103(a) as being unpatentable over Thaller alone or in view of Cowman. (Ans. 3.)

2. Thaller teaches "the sequence of the *aph*A gene (page 193, Figure 1)." (Ans. 3.)

3. Thaller "further characterize 5'- nucleotidase activity of the *E. coli* AphA enzyme (page 195, Table 1)." *Id.*

4. Thaller teaches that "another 5'-nucleotidase in *E. coli* is UshA (page 197, 2nd column, last paragraph). They suggest producing strains carrying aphA mutations (page 198)." *Id.*

5. Cowman "teach[es] the ushA gene from *E. coli* encoding a 5'-nucleotidase." *Id.*

6. The Examiner concludes that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce E. *coli* mutants having non-functional, for example, disrupted *ush*A gene and *aph*A gene. The motivation to produce such mutants is provided by Thaller et al. who teach 5'-nucleotide dephosphorylating activity of *ush*A gene and *aph*A gene. Mutants with disrupted *ush*A gene and *aph*A gene would have a higher yield of 5'-nucleotides.

Id. at 4.

7. The Examiner concludes that "[o]ne of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because the structures of both *ush*A gene and *aph*A gene were known at the time the invention was made and methods for disrupting known genes were widely used." *Id.*

8. Claims 9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thaller et al. alone or in view of Cowman et al. and further in view of Matsui et al. *Id.*

9. Matsui teaches

> [A] method for producing purine nucleosides such as inosine and guanosine which are important as intermediate compounds for synthesis of 5'-inosinic acid and 5'- guanylic acid (page 2, [001], lines 5-7). They teach a microorganism which acquired the purine nucleoside-producing ability because of an increase of an activity of an enzyme involved in the purine nucleoside biosynthesis due to its gene overexpression (page 2, [0007]).

(Ans. 4.)

10. Matsui teaches "that enzyme can be PRPP amidotransferase that is desensitized (page 2, [0008])." *Id.*

11. Matsui teaches "the mutation Lys326Glu in PRPP amidotransferase gene (*pur*F) resulting in desensitizing the feedback inhibition (page 6, [0055]; page 10, [0076])) and *E. coli* comprising said mutant PRPP amidotransferase (page 11)." *Id.* at 4-5.

12. Matsui "further teach[es] that in order to efficiently utilize the *pur*F gene, it can be used with other genes involved in the IMP biosynthesis such as IMP dehydrogenase gene (*gua*B) and GMP synthetase gene (*gua*A) (page 7, [0064])." *Id.* at 5.

13. The Examiner concludes that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce E. *coli* mutants having non-functional, for example, disrupted *ush*A gene and *aph*A gene thus preventing the decomposition of inosine 5'- phosphate ester and guanosine 5'-phosphate ester and additional genes such as *pur*F, *gua*A and *gua*B that increase their production.

Id.

14. The Examiner concludes that "[t]he motivation to produce such mutants is provided by Thaller et al. who teach 5'-nucleotide dephosphorylating

activity of *ush*A gene and *aph*A gene and Matsui et al. who teach the role of *pur*F, *gua*A and *gua*B in the nucleotide biosynthesis." (Ans. 5.)

15. The Examiner concludes that "[o]ne of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because the structures of all involved genes were known at the time the invention was made and methods for mutation of known genes were widely used." *Id.*

PRINCIPLES OF LAW

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant. In order to determine whether a prima facie case of obviousness has been established, we considered the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996); (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

ANALYSIS

Appellants contend that there is no teaching in Thaller that "decreasing expression of the gene would lead to enhanced production of nucleoside 5'-phosphate esters." (App. Br. 3.) Appellants further argue there is no teaching in Cowman that "decreasing expression of the gene would lead to enhanced production of nucleoside 5'phosphate esters." *Id.* Appellants further argue that neither Thaller nor Cowman "suggest

disrupting expression of the *ush*A and *aph*A genes, respectively, to [sic] for the purpose of preparing nucleoside 5'-phosphate esters." *Id.* Appellants argue that the cited references fail to suggest that decreasing expression of the ushA and aphA genes by mutating or disrupting those genes alone would substantially eliminate the 5'-nucleotidase activity in the periplasm, as claimed. (Reply Br. 1.)

The Examiner responds, arguing that

> [I]t would have been reasonable to expect that the elimination of enzymes (*aph*A and *ush*A) that decompose the product (nucleoside 5'-phosphate ester)… would be beneficial for the production of the product . . . . No unexpected results have been shown or argued by Appellant.

(Ans. 6.)

We find the Appellants have the better argument. The Examiner may be correct that the genes in the cited references encode enzymes that degrade nucleoside 5'-phosphate ester. However, we do not find that the Examiner has provided adequate evidence that one of ordinary skill in the art was provided a sufficient suggestion from Thaller, Cowman, and/or Matsui that a decrease in production of the *ushA* and *aphA* genes would substantially eliminate the 5'-nucleotidase activity in the periplasm, as claimed.

We therefore do not agree with the Examiner that the cited references suggest the claimed fermentation method of producing a nucleoside 5'-phosphate ester in which expression of the ushA and aphA gene is decreased. We do not find that Matsui overcomes the deficiencies of the combination of Thaller and Cowman. The appealed obviousness rejections are therefore reversed.

REVERSED

cdc

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